

## I CLAIM:

1. A composition of matter comprising a plurality of cells containing a diverse population of expressible oligonucleotides operationally linked to expression elements, said expressible oligonucleotides  
5 having a desirable bias of random codon sequences produced from random combinations of first and second oligonucleotide precursor populations having a desirable bias of random codon sequences.
2. The composition of claim 1, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is unbiased.
3. The composition of claim 1, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is biased toward a predetermined sequence.
4. The composition of claim 1, wherein said first and second oligonucleotides having random codon sequences have at least one specified codon at a predetermined position.
5. The composition of claim 1, wherein said cells are procaryotes.
6. The composition of claim 1, wherein said cells are E. coli.

7. A kit for the preparation of vectors useful for the expression of a diverse population of random peptides from combined first and second oligonucleotides having a desirable bias of random codon sequences,  
5 comprising: two vectors: a first vector having a cloning site for said first oligonucleotides and a pair of restriction sites for operationally combining first oligonucleotides with second oligonucleotides; and a  
10 second vector having a cloning site for said second oligonucleotides and a pair of restriction sites complementary to those on said first vector, one or both vectors containing expression elements capable of being operationally linked to said combined first and second oligonucleotides.

8. The kit of claim 7, wherein said vectors are in a filamentous bacteriophage.

9. The kit of claim 8, wherein said filamentous bacteriophage are M13.

10. The kit of claim 7, wherein said vectors are plasmids.

11. The kit of claim 7, wherein said vectors are phagemids.

12. The kit of claim 7, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is unbiased.

13. The kit of claim 7, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is diverse but biased toward a predetermined sequence.

14. The kit of claim 7, wherein said first and second oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

15. The kit of claim 7, wherein said pair of restriction sites are Fok I.

16. A cloning system for expressing random peptides from diverse populations of combined first and second oligonucleotides having a desirable bias of random codon sequences, comprising: a set of first vectors  
5 having a diverse population of first oligonucleotides having a desirable bias of random codon sequences and a set of second vectors having a diverse population of second oligonucleotides having a desirable bias of random codon sequences, said first and second vectors each  
10 having a pair of restriction sites so as to allow the operational combination of first and second oligonucleotides into a contiguous oligonucleotide having a desirable bias of random codon sequences.

17. The cloning system of claim 16, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is unbiased.

18. The cloning system of claim 16, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is diverse but biased toward a predetermined sequence.

19. The cloning system of claim 16, wherein said first and second oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

20. The cloning system of claim 16, wherein said combined first and second vectors is through a pair of restriction sites.

21. The cloning system of claim 16, wherein said pair of restriction sites are Fok I.

22. A composition of matter comprising a plurality of cells containing a diverse population of expressible oligonucleotides operationally linked to expression elements, said expressible oligonucleotides  
5 having a desirable bias of random codon sequences.

23. The composition of claim 22, wherein said cells are procaryotes.

24. The composition of claim 22, wherein said expressible oligonucleotides are expressed as peptide fusion proteins on the surface of a filamentous bacteriophage.

25. The composition of claim 22, wherein said filamentous bacteriophage is M13.

26. The composition of claim 22, wherein said fusion protein contains the product of gene VIII.

27. The composition of claim 22, wherein said diverse population of oligonucleotides having a desirable bias of random codon sequences are produced from the combination of diverse populations of first and second  
5 oligonucleotides having a desirable bias of random codon sequences.

28. The composition of claim 22, wherein the desirable bias of random codon sequences of said oligonucleotides is unbiased.

29. The composition of claim 22, wherein the desirable bias of random codon sequences of said oligonucleotides is diverse but biased toward a predetermined sequence.

30. The composition of claim 22, wherein said oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

31. A plurality of vectors containing a diverse population of expressible oligonucleotides having a desirable bias of random codon sequences.

32. The vectors of claim 31, wherein said oligonucleotides are expressible as fusion proteins on the surface of filamentous bacteriophage.

33. The vectors of claim 31, wherein said filamentous bacteriophage is M13.

34. The vectors of claim 31, wherein said fusion protein contains the product of gene VIII.

35. The vectors of claim 31, wherein the desirable bias of random codon sequences of said oligonucleotides is unbiased.

36. The vectors of claim 31, wherein the desirable bias of random codon sequences of said oligonucleotides is diverse but biased toward a predetermined sequence.

37. The vectors of claim 31, wherein said oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

38. A composition of matter, comprising a diverse population of oligonucleotides having a desirable bias of random codon sequences produced from random combinations of two or more oligonucleotide precursor  
5 populations having a desirable bias of random codon sequences.

39. A method of constructing a diverse population of vectors having combined first and second oligonucleotides having a desirable bias of random codon sequences capable of expressing said combined  
5 oligonucleotides as random peptides, comprising the steps of:

- 10 (a) operationally linking sequences from a diverse population of first oligonucleotides having a desirable bias of random codon sequences to a first vector;
- 15 (b) operationally linking sequences from a diverse population of second oligonucleotides having a desirable bias of random codon sequences to a second vector; and
- 20 (c) combining the vector products of steps (a) and (b) under conditions where said populations of first and second oligonucleotides are joined together into a population of combined vectors capable of being expressed.

40. The method of claim 39, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is unbiased.

41. The method of claim 39, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is diverse but biased toward a predetermined sequence.

42. The method of claim 39, wherein said first and second oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

43. The method of claim 38, wherein steps (a) through (c) are repeated two or more times.

44. A method of selecting a peptide capable of being bound by a ligand binding protein from a population of random peptides, comprising:

- 5 (a) operationally linking a diverse population of first oligonucleotides having a desirable bias of random codon sequences to a first vector;
- 10 (b) operationally linking a diverse population of second oligonucleotides having a desirable bias of random codon sequences to a second vector;
- 15 (c) combining the vector products of steps (a) and (b) under conditions where said populations of first and second oligonucleotides are joined together into a population of combined vectors;
- 20 (d) introducing said population of combined vectors into a compatible host under conditions sufficient for expressing said population of random peptides; and
- (e) determining the peptide which binds to said ligand binding protein.



45. The method of claim 44, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is unbiased.

46. The method of claim 44, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is diverse but biased toward a predetermined sequence.

47. The method of claim 44, wherein said first and second oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

48. The method of claim 44, wherein steps (a) through (c) are repeated two or more times.

49. A method for determining the nucleic acid sequence encoding a peptide capable of being bound by a ligand binding protein which is selected from a population of random peptides, comprising:

- 5           (a) operationally linking a diverse population of first oligonucleotides having a desirable bias of random codon sequences to a first vector;
- 10           (b) operationally linking a diverse population of second oligonucleotides having a desirable bias of random codon sequences to a second vector;
- 15           (c) combining the vector products of steps (a) and (b) under conditions where said populations of first and second oligonucleotides are joined together into a population of combined vectors;
- 20           (d) introducing said population of combined vectors into a compatible host under conditions sufficient for expressing said population of random peptides;
- (e) determining the peptide which binds to said ligand binding protein;
- 25           (f) isolating the nucleic acid encoding said peptide; and
- (g) sequencing said nucleic acid.

50. The method of claim 49, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is unbiased.

51. The method of claim 49, wherein the desirable bias of random codon sequences of said first and second oligonucleotides is diverse but biased toward a predetermined sequence.

52. The method of claim 49, wherein said first and second oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

53. The method of claim 49, wherein steps (a) through (c) are repeated two or more times.

54. A method of constructing a diverse population of vectors containing expressible oligonucleotides having a desirable bias of random codon sequences, comprising operationally linking a diverse  
5 population of oligonucleotides having a desirable bias of random codon sequences to expression elements.

55. The method of claim 54, wherein said oligonucleotides are expressible as fusion proteins on the surface of filamentous bacteriophage.

56. The method of claim 54, wherein said filamentous bacteriophage are M13.

57. The method of claim 54, wherein said fusion protein contains the product of gene VIII.

58. The method of claim 54, wherein the desirable bias of random codon sequences of said oligonucleotides is unbiased.

59. The method of claim 54, wherein the desirable bias of random codon sequences of said oligonucleotides is diverse but biased toward a predetermined sequence.

60. The method of claim 54, wherein said oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

61. The method of claim 54, wherein said operationally linking further comprising the steps of:

(a) operationally linking a diverse population of first oligonucleotides having a desirable bias of random codon sequences to a first vector;

(b) operationally linking a diverse population of second oligonucleotides having a desirable bias of random codon sequences to a second vector; and

(c) combining the vector products of steps (a) and (b) under conditions where said populations of first and second oligonucleotides are joined together into a population of combined vectors.

62. The method of claim 61, wherein steps (a) through (c) are repeated two or more times.

63. A method of selecting a peptide capable of being bound by a binding protein from a population of random peptides, comprising:

- 5 (a) operationally linking a diverse population of oligonucleotides having a desirable bias of random codon sequences to expression elements;
- 10 (b) introducing said population of vectors into a compatible host under conditions sufficient for expressing said population of random peptides; and
- (c) determining the peptide which binds to said ligand binding protein.

64. The method of claim 63, wherein said population of random peptides are expressed as fusion proteins on the surface of filamentous bacteriophage.

65. The method of claim 63, wherein said filamentous bacteriophage are M13.

66. The method of claim 63, wherein said fusion protein contains the product of gene VIII.

67. The method of claim 63, wherein the desirable bias of random codon sequences of said oligonucleotides is unbiased.

68. The method of claim 63, wherein the desirable bias of random codon sequences of said oligonucleotides is diverse but biased toward a predetermined sequence.

69. The method of claim 63, wherein said oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

70. The method of claim 63, wherein step (a) further comprises:

5 (a1) operationally linking a diverse population of first oligonucleotides having a desirable bias of random codon sequences to a first vector;

10 (a2) operationally linking a diverse population of second oligonucleotides having a desirable bias of random codon sequences to a second vector; and

15 (a3) combining the vector products of steps (a) and (b) under conditions where said populations of first and second oligonucleotides are joined together into a population of combined vectors.

71. The method of claim 70, wherein steps (a1) through (a3) are repeated two or more times.

72. A method of determining the nucleic acid sequence encoding a peptide capable of being bound by a ligand binding protein which is selected from a population of random peptides, comprising:

- 5           (a) operationally linking a diverse population of oligonucleotides having a desirable bias of random codon sequences to expression elements.
- 10          (b) introducing said population of vectors into a compatible host under conditions sufficient for expressing said population of random peptides;
- (c) determining the peptide which binds to said ligand binding protein;
- 15          (d) isolating the nucleic acid encoding said peptide; and
- (e) sequencing said nucleic acid.

73. The method of claim 72, wherein said population of random peptides are expressed as fusion proteins on the surface of filamentous bacteriophage.

74. The method of claim 72, wherein said filamentous bacteriophage are M13.

75. The method of claim 72, wherein said fusion protein contains the product of gene VIII.

76. The method of claim 72, wherein the desirable bias of random codon sequences of said oligonucleotides is unbiased.

77. The method of claim 72, wherein the desirable bias of random codon sequences of said oligonucleotides is diverse but biased toward a predetermined sequence.

78. The method of claim 72, wherein said oligonucleotides having a desirable bias of random codon sequences have at least one specified codon at a predetermined position.

79. The method of claim 72, wherein step (a) further comprises:

(a1) operationally linking a diverse population of first oligonucleotides having a desirable bias of random codon sequences to a first vector;

(a2) operationally linking a diverse population of second oligonucleotides having a desirable bias of random codon sequences to a second vector; and

(a3) combining the vector products of steps (a) and (b) under conditions where said populations of first and second oligonucleotides are joined together into a population of combined vectors.

80. The method of claim 78, wherein steps (a1) through (a3) are repeated two or more times.

81. A vector comprising two copies of a gene encoding a filamentous bacteriophage coat protein, both copies encoding substantially the same amino acid sequence but having different nucleotide sequences.



83. The vector of claim 81, wherein said gene is gene VIII.

85. A vector comprising two copies of a gene encoding a filamentous bacteriophage coat protein, one copy of said gene capable of being operationally linked to an oligonucleotide wherein said oligonucleotide can be expressed as a fusion protein on the surface of said filamentous bacteriophage or as a soluble peptide.

87. The vector of claim 84, wherein said bacteriophage coat protein is M13 gene VIII.

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